

RECALCITRANT LEG ULCERS AS THE ONLY MANIFESTATION OF ESSENTIAL TYPE 2 CRYOGLOBULINEMIA



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INTRODUCTION

Chronic leg ulcers are a disabling condition with great impact on patient's quality of life and health care costs^{1,2}. Venous, arterial or mixed insufficiency and neuropathy are the main etiologic factors in 80-95% of the cases^{3,4}. In the remaining cases other etiologies might be considered.

Mixed Cryoglobulinemia is an immunocomplex-mediated systemic vasculitis associated with chronic infections (in particular Hepatitis C virus (HCV)), B-cell lymphoproliferative diseases and autoimmune disorders.

In 39-48% cases an underlying etiology is not found, thus the designation Essential Mixed Cryoglobulinemia^{5,6}.

Clinical manifestations are mainly cutaneous – purpura (75%), ulcers (16%) and necrosis (14%), but also neurologic – mainly peripheral neuropathy (52%), renal (35-75%) and arthralgia/arthritis (44%)^{5,7}.

Therapeutic options include systemic corticosteroids, plasmapheresis and immunosuppressive agents, particularly cyclophosphamide and rituximab, with significant side effects and variable response rates^{5,6,8}.

CASE REPORT

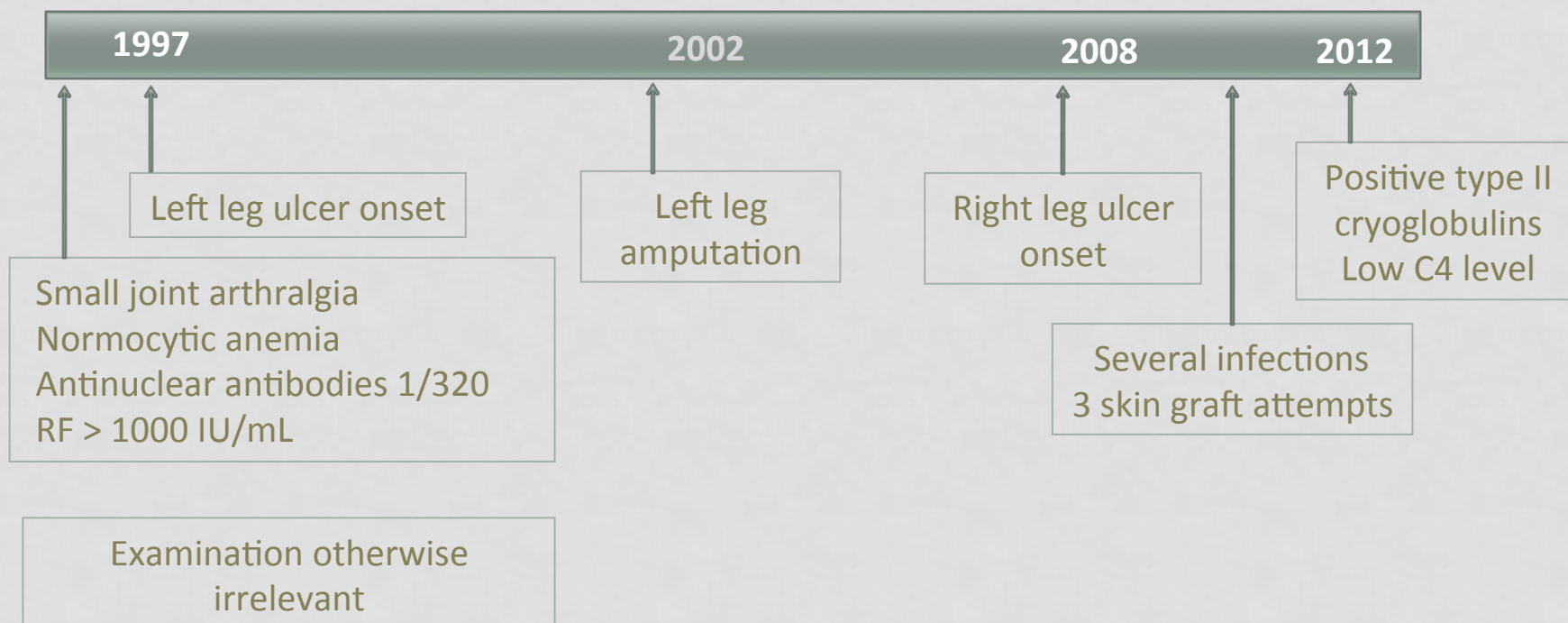


Figure 1 – Chronologic evolution of the clinical picture

CASE REPORT

Female 60-year-old patient healthy until her 46 years (1997), when she was diagnosed with undifferentiated connective tissue disease (Fig. 3) for which azathioprine and low dose prednisolone were started. Soon after she developed a progressive enlarging ulcer on the left leg, which led to left leg amputation 5 years later.

In 2008 she was referred to our center due to a new right leg ulcer, which progressed to circumferential involvement (Fig 2-3) despite multiple treatments – antibiotics when indicated, vacuum-assisted closure therapy and skin grafting. Immunosuppressive therapy was stopped as there were no criteria for connective tissue disease, albeit she kept high Rheumatoid Factor (RF) and normocytic anemia along this time.



Figure 2 – Right leg ulcer in 2012 when cryoglobulinemia diagnosis was established

CASE REPORT



Figure 3 – Right leg ulcer in 2012 when cryoglobulinemia diagnosis was established

Recently type II cryoglobulins became positive (though negative in previous evaluations), with complement consumption (low C4) and negative HCV. The remaining autoimmunity panel was also negative. Renal and neurologic evaluations were unremarkable.

She had no history of diabetes mellitus, arterial hypertension, dyslipidemia or smoking habits. No evidence of arterial or venous insufficiency on several Color Doppler Ultrasound evaluations was found.

The patient is now on monthly cyclophosphamide and metilprednisolone pulse therapy, in combination with plasmapheresis, with progressive improvement.

DISCUSSION

Essential mixed cryoglobulinemia is a challenging condition as it can present itself with atypical manifestations, therefore delaying the diagnosis establishment and proper therapeutic approach. Additionally, as cryoglobulinemia diagnosis is predominantly based on the laboratory demonstration of serum cryoglobulins⁹, ideal temperature sample conditions are mandatory for correct laboratorial testing¹⁰. Otherwise, false negatives might occur, which can hamper a correct diagnosis.

Although our patient lacked other manifestations such as cutaneous purpura, renal or neurologic involvement and severe cryoglobulinemia typically encompasses renal disease, its absence could not exclude the diagnosis.

Strong clinical suspicion, maintained high RF level and complement consumption were key diagnosis clues.

It is unlikely that our patient had persistent cryoglobulinemia for 14 years without other organ involvement. It remains to be determined whether the left leg ulcer was secondary to the undifferentiated connective tissue disease or to another unidentified cause.

During the last years we did several attempts to identify serum cryoglobulins, but only recently were we able to do so. Thus, the importance of repeating cryoglobulins measurement deserves enhanced attention when the clinical picture is suggestive and other laboratorial parameters are consistent with this diagnosis.

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